Remarks/Arguments:

Claims 2-3, 7-8, 28, 37, 45, 47, 59, 61, 81-82, and 85-92 are canceled without prejudice. Claims 1, 6, 26-27, 35-36, 44, 46, 58, and 60 are amended. More specifically, claims 1, 6, 26, 35, 44, and 58 are amended by incorporating the limitations from claims 81, 82, 86, 88, 90, and 92, respectively. Claim 27 is amended by incorporating the limitations from claims 26, 28, and 85-86. Claim 36 is amended by incorporating the limitations from claims 35, 37, and 87-88. Claim 46 is amended by incorporating the limitations from claims 44, 47, and 89-90. Claim 60 is amended by incorporating the limitations from claims 58, 61, and 91-92. Claims 35 and 58 are also amended to correct minor typographical errors. No new matter is introduced.

Claims 1, 6, 12-13, 26-27, 35-36, 44, 46, 52-53, 58, 60, and 74 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

CLAIM OBJECTIONS

Claims 35-37, 58-61, 87-88, and 91-92 are objected to because claims 35 and 58 recite "interferon, alpha-2b." Applicants have deleted the extra comma in this term.

Claim 58 is further objected to because it recites "a round melanoma biochemotherapy." Applicants have replaced the term with "a round of melanoma biochemotherapy."

In light of the foregoing, Applicants respectfully submit that the objections are overcome and should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 27-28, 36-37, 46-47, 60-61, and 87-92 are rejected as being indefinite for reciting inconsistent terms in independent claims and their dependent claims.

Applicants have amended claims 27, 36, 46, and 60 such that they no longer depend from claims 26, 35, 44, and 58, respectively. Claims 28, 37, 47, 61, and 87-92 have been canceled without prejudice.

In light of the foregoing, Applicants respectfully submit that the rejections are overcome and should be withdrawn.

CLAIM REJECTION UNDER 35 USC § 102(b)

Claim 26 is rejected as being anticipated by Soengas et al. (2001) Nature 409:207-211 ("Soengas"). Applicants respectfully traverse.

Claim 26 is directed to a method of monitoring melanoma progression. The method comprises providing a melanoma tissue sample or a blood sample containing DNA from a human subject suffering from melanoma and analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA. The loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates the progression of melanoma in the subject.

As presented in Applicants' previous responses to Office Actions, Soengas compares the expression of APAF-1 in metastatic and primary melanoma samples and speculated without any evidence that loss of APAF-1 may be associated with disease progression (page 207, right column, line 20 – page 208, left column, line 4). However, the expression of APAF-1 does not necessarily correlate with LOH of APAF-1 (Figure 3 of the present specification and Soengas, page 207, right column, Figures 1b and 1c, sample 6) or LOH of D12S1657, D12S393, D12S1706, or D12S346 (Soengas, page 207, right column, Figures 1b and 1c, samples 6 and 16).

Further, in Soengas, the APAF-1 gene was mapped to a position between D12S1657 and D12S393. As pointed out at page 28, line 27 – page 29, line 6 of the present specification, the correct location of the APAF-1 gene is between D12S1706 and D12S346. Because Soengas mapped the APAF-1 gene to a location more than 0.3 Mb away from the correct location, the relationship between the microsatellite markers and the APAF-1 gene was significantly wrong in Soengas. Consequently, if

one skilled in the art relies on the value of the LOH of APAF-1 as determined in Soengas to predict the progression of melanoma, the prediction would not be correct.

Therefore, Soengas cannot anticipate claim 26, because it fails to teach the association of LOH of D12S1657, D12S393, D12S1706, or D12S346 with melanoma progression. Applicants thus respectfully request that the rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 103

(1) Claims 1-3, 6-8, 12-13, 74, and 81-82 are rejected as being unpatentable over Soengas in view of U.S. Patent No. 6,156,504 to Gocke et al. ("Gocke"). Applicants respectfully traverse.

Among the rejected claims, claims 1 and 6 are independent claims. Claims 1 and 6 involve detecting or analyzing one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on DNA existing as acellular DNA in a human subject. As presented in Applicants' previous responses to Office Actions, Soengas analyzes D12S1657, D12S393, D12S1706, and D12S346 on cellular DNA from melanoma samples. Gocke discloses the detection of extracellular tumor-associated nucleic acid in blood plasma or serum in general, but does not suggest at all the detection of D12S1657, D12S393, D12S1706, or D12S346 on acellular DNA. Since neither Soengas nor Gocke indicates the presence of D12S1657, D12S393, D12S1706, or D12S346 on acellular DNA, one skilled in the art would not have reasonably expected that D12S1657, D12S393, D12S1706, or D12S346 could be detected on acellular DNA because of the unpredictable nature of acellular DNA in a human body.

Therefore, claims 1 and 6 (as well as claims 12-13 and 74 dependent from claim 1 or 6) are non-obvious over the cited art at least for lack of reasonable expectation of success. Claims 2-3, 7-8, and 81-82 have been canceled without prejudice. Withdrawal of the rejections is thus respectfully requested.

(2) Claims 35 and 58-59 are rejected as being unpatentable over Soengas in view of O'Day et al. (1999) Journal of Clinical Oncology 17:2752-2761 ("O'Day"). Applicants respectfully traverse.

Claim 35 is directed to a method of predicting the efficacy of a melanoma biochemotherapy. The method comprises providing a melanoma tissue sample or a blood sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of a biochemotherapy and analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA. The biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen. The loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy in the subject.

Claim 58 is directed to a method of determining the probability of responsiveness to a round of melanoma biochemotherapy. The method comprises providing a melanoma tissue sample or a blood sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of biochemotherapy and analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA. The biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen. The loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy in the subject.

As presented in Applicants' previous responses to Office Actions, claims 35 and 58 relate to the association of LOH of D12S1657, D12S393, D12S1706, or D12S346 with poor efficacy of a melanoma biochemotherapy or a low probability of responsiveness to the biochemotherapy in a human subject. In contrast, Soengas discloses that APAF-1 negative melanoma cell lines are resistant to ADR, a chemotherapeutic agent (page 209, left column, lines 8-10).

APAF-1 negative cells are cells expressing little APAF-1 (Soengas, page 208, left column, line 10). As discussed above, the expression of APAF-1 does not

necessarily correlate with LOH of D12S1657, D12S393, D12S1706, or D12S346. Further, it is well known in the art that in vitro experiments do not necessarily reflect the conditions in vivo. As such, Soengas cannot render obvious claim 35 or 58, because it fails to teach the association of LOH of D12S1657, D12S393, D12S1706, or D12S346 with poor efficacy of a melanoma biochemotherapy or a low probability of responsiveness to the biochemotherapy in a human subject.

O'Day cannot cure the defect of Soengas, and was not relied on by the Examiner for such. Instead, O'Day was relied on by the Examiner for teaching a biochemotherapy comprising dacarbazine, cisplatin, vinblastin, interferon alpha-2b, IL-2, and tamoxifen.

Therefore, claims 35 and 58 are non-obvious over the cited art at least for lack of reasonable expectation of success. Claim 59 has been canceled without prejudice. Withdrawal of the rejections is thus respectfully requested.

(3) Claims 44-45 are rejected as being unpatentable over Soengas in view of Taback et al. (2001) Cancer Research 61:5723-5726 ("Taback"). Applicants respectfully traverse.

Claim 44 is directed to a method of determining the probability of survival. The method comprises providing a melanoma tissue sample or a blood sample containing DNA from a human subject suffering from a stage III or IV melanoma and analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA. The loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the subject has a low probability of surviving melanoma.

Soengas discloses the inactivation of APAF-1 in metastatic melanoma (page 207, left column, Abstract). It suggests nothing about the association of LOH of D12S1657, D12S393, D12S1706, or D12S346 with a low probability of surviving melanoma. As such, Soengas cannot render claim 44 obvious.

Taback cannot cure the defect of Soengas, and was not relied on by the Examiner for such. Instead, Taback was relied on by the Examiner for teaching the

association of LOH of some microsatellite markers in stages III and IV melanoma with a decreased probability of survival. However, the microsatellite markers tested in Taback are not D12S1657, D12S393, D12S1706, or D12S346.

Therefore, claim 44 is non-obvious over the cited art at least for lack of reasonable expectation of success. Claim 45 has been canceled without prejudice. Withdrawal of the rejections is thus respectfully requested.

(4) Claims 52-53 are rejected as being unpatentable over Soengas in view of Taback, and further in view of Yu et al. (1999) Cancer 86:612-627 ("Yu"). Applicants respectfully traverse.

Claims 52-53 depend from claim 44. As mentioned above, Soengas and Taback, either alone or in combination, cannot render claim 44 obvious. Yu cannot cure the defects of Soengas and Yu, and was not relied on by the Examiner for such. Instead, Taback was relied on by the Examiner for teaching RLM and ITM.

Therefore, claim 44 is non-obvious over the cited art at least for lack of reasonable expectation of success. So are claims 52-53 dependent from claim 44. Withdrawal of the rejections is thus respectfully requested.

CONCLUSION

Applicants believe the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). In this connection, these amendments were not earlier presented because they are in response to the matters pointed out for the first time in the final Office Action. Lastly, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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